EUROPEAN JOURNAL OF CANCER 44 (2008) 2555–2572

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Inoperable colorectal liver metastases: A declining entity?

*G. Garcea**, *S.L. Ong*, *G.J. Maddern*

Department of Hepatobiliary and Upper Gastrointestinal Surgery, The Queen Elizabeth Hospital, 28 Woodville Road, Adelaide, SA 5011, Australia

ARTICLE INFO

Article history:
Received 5 June 2008
Received in revised form 14 July 2008
Accepted 17 July 2008
Available online 26 August 2008

Keywords:
Colorectal hepatic metastases
Ex vivo resection
Chemotherapy
Hepatic artery infusion
Radiotherapy
Ablation

ABSTRACT

Background: Untreated colorectal liver metastases (CLMs) have a dismal prognosis. Surgery remains the gold standard of treatment, but many patients will have inoperable disease at presentation. Until recently, the outlook for such patients was bleak. The purpose of this review was to report on available options in the treatment CLMs, which would be considered unresectable by conventional evaluation.

Methods: Inclusion criteria were articles published in English-language journals reporting on either retrospective or prospective cohorts of patients undergoing treatment for conventionally inoperable CLM. Main outcome measures were survival, resectability rates, morbidity and mortality following treatment of the patients' disease.

Results: Improved chemotherapy regimes and other innovative treatments have opened up new options for such patients and may even render conventionally inoperable disease resectable. The aim of treatment should be down-staging of metastases to achieve resectability, however, other treatments such as ablation may be also be used (either alone or in conjunction with resection).

Conclusion: A nihilistic attitude to the patient with seemingly inoperable liver metastases should be discouraged. Discussion of such patients at multi-disciplinary meetings is essential in order to plan and monitor treatments.

1. Introduction

Colorectal cancer (CRC) is the second most common malignancy in the United Kingdom[1] and the third most common malignancy in the world.[2] It accounts for approximately 10% of all cancer-related death.[1] Early resection of primary lesions without distant spread gives an excellent prognosis, but many patients present with more extensive disease. The liver is the most common site for blood-borne metastases, particularly for malignancies arising in organs drained by the portal circulation. Despite continuing efforts towards early detection of colorectal cancer, up to 35% of patients have hepatic disease at the time of operation for the primary lesion.[3,4] A further 20% will develop hepatic lesions after resection of the primary tumour.[5,6] The prognosis for untreated colorectal liver metastases (CLMs) is uniformly poor, with a median survival of less than 12 months and a 5-year survival rate of near zero.[7,8] This progressive involvement of the liver from colorectal cancer may be the major or sole factor determining survival (NIH consensus 1990, Wood 1976, August 1985).

Surgical resection represents the only hope of cure for CLM and, though currently possible in only 15–25% of patients, yields 5-year survival rates approaching 30–50%.[5,9–12] Incom-

* *Corresponding author.*
E-mail address: gg43@le.ac.uk (G. Garcea).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.07.028

plete resection of CLM is associated with the same prognosis as patients without resection.[13]

2. Methods

The purpose of this review is to report on treatments available in the treatment and assessment of CLM, which would be considered unresectable by conventional evaluation. A Pubmed-based web search was undertaken using the keywords colorectal hepatic metastases, unresectable, inoperable, *ex vivo* resection, chemotherapy, hepatic artery infusion, radiotherapy, staging and ablation. Inclusion criteria were articles published in English-language journals reporting on either retrospective or prospective cohorts of patients undergoing treatment for conventionally inoperable CLM. Main outcome measures were survival, resectability rates, morbidity and mortality following treatment of the patients' disease.

3. Factors determining resectability of crc hepatic metastases

The criteria determining the resectability of CLM have been continually evolving over the last 10 years due largely to the improvements in surgical technique and chemoradiotherapy advances. The aim of liver resection is to remove all macroscopic disease with negative resection margins and leave sufficient functioning liver,[14] with preservation of vascular inflow and outflow. The acceptable residual functioning volume should be approximately 20% of the standard liver volume or the equivalent of a minimum of two segments[14] in patients without normal liver parenchyma. This obligate functional volume has been estimated as 30–60% in patients with chemotherapy steatosis or hepatitis and 40–70% in cases of cirrhosis.[15] Previously, the goal of margin status was a 1 cm clearance after the resection of CLM, following the previous reports that resection margins of greater than 1 cm were associated with better survival rates.[16,17] However, there is emerging evidence that provided resection margins are microscopically free of tumour, an improvement in survival is still evident when compared to positive resections margins (64% *versus* 17% 5-year survival).[18,19]

3.1. Tumour number

Previous studies evaluating long-term survival from CLM resection have cited tumour number as a poor prognostic indicator,[16,17] and hence the presence of 4 or above lesions was traditionally seen as a relative contraindication to resection. Algorithms such as the risk score by Fong *and colleagues* have also incorporated the number of metastases in predicting outcome survival and outcome after resection.[20–22] However, it is now clear that provided that negative resection margins can be achieved, survival is not affected by the number of CLM.[23] It has been postulated that this achievement is secondary to thorough intraoperative evaluation, including intraoperative ultrasound, to pick up any lesions not evident on pre-operative staging.[24] Hence, the number of CLM should not be regarded as a contraindication to resection, provided that the sufficient functional liver remains post-operatively, although the presence of numerous liver lesions does negatively impact on long-term survival post-operatively.

3.2. Tumour size

A maximum tumour size of above 5 cm in diameter has been associated with a poorer survival,[5,22,25] probably as a reflection of overall tumour burden. However, there is evidence that provided a negative resection margin can be achieved, even metastases as large as 8 cm can be removed with a long-term survival equivalent to smaller lesions.[26] Larger metastases can frequently make liver resection technically more difficult but do not represent an obstacle to surgery in terms of survival benefit.

3.3. Tumour location

Whilst formal data regarding tumour location and resectability rates are scarce, the position of a CLM near major inflow or drainage structures within the liver is indirectly a major determinant in influencing the probability of successfully resecting these lesions. Tumour location next to major vessels, such as the inferior vena cava, increases the technical difficulty of excision. Alternatively, tumour location near major inflow or drainage structures may compromise tumour resectability by influencing the volume of normal liver removed subsequent to sacrificing its blood supply. Bi-lobar metastases present difficulties for this reason also.

3.4. Extra-hepatic pulmonary disease

Resection of isolated pulmonary metastases from colorectal adenocarcinoma is now accepted treatment with a reported 5-year survival of approximately 40–50%[27–30] and post-operative mortality of less than 1%.[31,32] Data from patients undergoing resections for metachronous presentations of pulmonary and hepatic disease also display a survival advantage to be gained from aggressive resection or multiple resections in these patients, with median and 5-year survivals comparable to resection of isolated pulmonary metastases.[33–35] Reports of resections after synchronous presentation of disease is more sparse, but most studies, with the exception of Nagakuri *and* colleagues[36] suggest that the presence of pulmonary metastases at the same time of presentation with CLM is not a contraindication to resection (Table 1).[37–42] Synchronous presentation of CLM with pulmonary metastases has been shown to have no difference in survival following resection when compared to metachronous disease.[43,44]

Prognostic factors for long-term survival following resection of pulmonary metastases include the presence of thoracic lymph node involvement and elevated carcinoembryonic antigen levels (CEA),[45–47] with some studies also reporting the number and laterality of pulmonary metastases to predict poor survival.[28,42,47] However, bearing these considerations in mind, the presence of limited pulmonary extra-hepatic disease, which is amenable to curative resection, is not a contraindication CLM resection. The timing of which resection should be undertaken first varies from centre to centre. By undertaking CLM resection first, un-suspected abdominal

Table 1 – Median and yearly survival following resection of synchronous CLM and hepatic metastases

Study	Year	Number of patients	Mortality	Yearly survival (%)				Median survival (months)	Follow-up (months)
				1 Year	2 Year	3 Year	5 Year		
Joosten et al.[37]	2008	39	–	–	81	–	20	13	38
Lee et al.[38]	2007	32	0	–	–	–	60.8	44.3	–
Tsukioka et al.[204]	2007	23	–	–	–	–	38	–	26
Miller et al.[39]	2007	31	–	91	–	31	19	39.6	79
Takahashi et al.[40]	2007	30	0	–	–	–	58	–	–
Reddy et al.[41]	2004	26	3.8	–	–	–	–	34.7	23.3
Nagakura et al.[36]	2001	10	Multivariate analysis showing that sequential detection strongest independent prognostic factor for survival				0	–	94

Median and yearly survival figures for stratified risk groups, based on prognostic markers.

extra-hepatic metastases may be discovered which would preclude pulmonary resection. Additionally, since pulmonary function does not fully recover following resection (unlike liver function) CLM resection should probably be first undertaken followed by thoracotomy.[48]

3.5. Extra-hepatic lymph node disease

Various studies have reported on the prognostic effect of micro-metastases to hilar lymph nodes following hepatic resection. For the purpose of this review, the focus lies on whether macroscopic disease evident within hilar lymph nodes should be a contraindication to hepatic resection. It is well accepted that any microscopic or macroscopic lymph node involvement negatively impacts on long-term survival.[49–52] As a consequence of this, many early studies considered hilar lymph node involvement as definite contraindication to CLM resection.[16] A systematic review by Rodgers and McCall examined the results of 15 studies reporting on survival rates following resection of CLM.[53] 145 patients from these studies had involved hilar lymph nodes macroscopically at the time of resection with only 5 of these alive at 5-years and only one with definite disease-free survival.[53] It would seem that the probability of achieving a curative resection with macroscopic lymph node involvement is low. Despite this, it may be that a survival benefit could be achieved even with macroscopic hilar lymph node disease, although the proportion of patients who would actually benefit is low. The location of involved lymph nodes must also be considered before undertaking CLM resection. Patients with hilar lymph node metastatic disease involving the hepatoduodenal or retro-pancreatic area are more likely to achieve long-term survival than patients with hepatic artery/celiac axis nodes (38% 3-year survival *versus* 0%).[54,55] At present then, it would appear that hilar lymph node involvement remains a relative contraindication to CLM resection.

3.5. *Extra-hepatic peritoneal metastases and other metastases*

Surgical resection combined with intraperitoneal chemotherapy for isolated peritoneal colorectal metastases has been reported by a randomised controlled trial with a suggested improvement in survival when compared to systemic chemotherapy alone (median survival of 22.3 and 12.6 months, respectively).[56] Whilst peritoneal invasion due to direct invasion of adjacent structures of a CLM would not be considered a contraindication to resection, provided that R0 resection margins could be achieved, the presence of distant peritoneal metastases has a very different outlook. A five-year survival of up to 32% has been reported following the resection of CLM and extra-hepatic metastases, although this survival represents a wide range of extra-hepatic disease ranging from pulmonary, hilar lymph node and peritoneal disease, as well as distant organs.[57] A study examining 61 patients undergoing CLM resection combined with cyto-reduction and intraperitoneal chemotherapy found an overall and disease-free survival of 19% and 10%, respectively.[58] However, combined resection of CLM and peritoneal disease is not the standard of care and as such the presence of this combined disease would be considered by most centres as a contraindication to attempted resection.

4. Pre-operative chemotherapy and down-staging

Chemotherapy is being increasingly used as a method of down-staging tumours in an attempt to reduce tumour volume to a size where resecting them may be considered. Chemotherapy alone will not completely eradicate CLM in general. Complete pathological responses have been reported but these are relatively rare with a complete response rate of approximately 7%.[59,60] Chemotherapy alone (particularly combination chemotherapy including oxaliplatin, irinotecan, oxaliplatin and leucovorin) has led to response rates of between 39% and 66% and median survivals of 14–26 months.[61–67] Hence, attempting a subsequent liver resection, in those patients who are suitably down-staged, must be carefully evaluated in terms of survival benefit *versus* surgical risk.

A number of regimens have been described in down-staging CLMs including systemic conventional therapy and regional intra-arterial chemotherapy, sometimes used in combination with other techniques to increase tumour vol-

Table 2 – Survival following surgical resection of CLM made resectable after down-staging systemic chemotherapy

Study	Year	Number of patients	Regimen	Additional agents	Response rate (%)	Resection rate (%)	Median survival (months)	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Adam et al.[a78]	2007	151	Irinotecan ± oxaliplatin	Cetumixab	–	7	20	–	–	–	–
Masi et al.[72]	2006	74	FOLFIRIFOX	–	71.6	25.5		4-year survival of 37%			
Folprecht et al.[77]	2006	20	5-FU and Irinotecan	Cetumixab	–	20	–	–	–	–	–
Ho et al.[68]	2005	40	FOLFIRI	–	55	10	Patients remained alive at mean follow-up of 33 months				
Alberts et al.[69]	2005	42	FOLFOX4	–	59.5	33.3	26_{DF}	–	–	–	–
Pozzo et al.[70]	2004	40	FOLFIRI	–	47.5	32.5	14.3_{DF}	–	–	–	–
Adam et al.[73]	2004	1104	Varying	–	12.5	12.5	39	–	–	52	33
Adam et al.[74]	2001	701	FOLFOX	–	–	13.6	36	–	–	–	34
Giacchetti et al.[71]	1999	151	FOLFOX	–	58.9	38.4	48	–	–	–	50
Bismuth et al.[75]	1996	53	FOLFOX	–	–	16.1	–	–	–	–	40
Fowler et al.[76]	1992	11	5-FU, Lecovarin	–	–	–	15 patients disease free at 15, 18 and 31 months				

DF = Disease free.
FOLFIRIXFOX = Oxaliplatin and 5-FU modulated by leucovorin.
FOFOX = 5-FU, leucovorin oxaliplatin and irinotecan.
FOLFIRI = 5-FU, leucovorin and irinotecan.
a Cohort of patients with resistance to standard chemotherapy.

ume such as portal vein embolisation or tumour embolisation.

4.1. *Systemic conventional chemotherapy*

Assessing the efficacy of down-staging chemotherapy for inoperable CLM must take into account both the resectability rates following therapy, i.e. the conversion rate from inoperable CLMs to operable ones, and the survival following resection. Resectability rates are confounded by tendency of studies to differ in their cohort analysis. Some reports will only include patients who are deemed inoperable due to tumour burden within the liver, whereas other studies will include a broader range of patients, including those with extra hepatic disease. Whilst down-staging to resectable disease is presumably not an uncommon event in clinical practice, few large-scale studies describing their experience with these patients are evident in the literature. Table 2 summarises the relevant data from Refs. [68–76]. Five-year survival following surgery has been reported as between 30% and 60%, with overall median survival of approximately 30 months and a disease-free median survival of 14–26 months.[68–76] Clearly salvage surgery after chemotherapy has the potential to achieve long-term survival in some patients, but the survival range overlaps significantly with upper-end of survivals reported with chemotherapy alone, hence patient selection for this approach is critical.

4.2. *Advances in chemotherapy agents*

The development of new anti-cancer compounds has offered further possibilities to down-stage CLM to a stage where resection may be considered. Cetuximab is a monoclonal antibody directed against epidermal growth factor receptor (EGFR) leading to apoptosis, inhibition of cell growth and angiogenesis.[77] Early data suggest that the addition of such new agents may render a further sub-group of patients operable (Table 2),[77,78] even those refractory to conventional chemotherapy regimens.[78] EGFR triggers two signalling cascades involved in cell proliferation (MAPK or PDK1-AKT pathways)[79] and there is emerging evidence that *K-RAS* mutations are associated with resistance to cetuximab therapy probably *via* activation of the MAPK pathway downstream from the point of action of cetuximab.[80] The implication of these findings is that it may be possible to select patients most likely to gain benefit from cetuximab chemotherapy, dependent on their *RAS* status and that chemotherapy targeted along several points of the EGFR and RAS/MAPK signalling pathways may maximise tumour response to these novel chemotherapeutic regimens.

Other agents have also shown promise in increasing response rates when used as combination treatments for patients with refractory disease to standard chemotherapy regimens, and could be used to increase the number of patients achieving sufficient down-staging to undergo resection. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Treatment with VEGF has resulted in response rates for 45–70% when combined with other conventional chemotherapy agents.[81,82] In addition, there are growing data that it is well tolerated, safe to use

prior resection surgery and may reduce the incidence of severe hepatic injury associated with conventional chemotherapeutic regimes.[83,84]

4.3. *Regional chemotherapy ± chemoembolisation*

Randomised trials have shown that hepatic arterial infusion therapy for unresectable hepatic metastases may result in improved survival rates than systemic therapy with 5-FU alone[81] and may also lead to improved quality of life in these patients.[82] The conversion rate to resectability is variable across the studies but would appear overall to be lower than after systemic chemotherapy (despite occasional reported resectability rates of up to 54% (Table 3).[83–90] Data on long-term survival are sparser than with systemic chemotherapy, but there appear to be similar 5-year survival rates of between 30% and 50% (Table 3). Despite the potential efficacy of hepatic arterial infusion therapy, technical problems have been reported such as thrombosis, catheter dislodgments, hepatitis, biliary sclerosis and duodenal ulceration, which may occur in up to 50% of treated patients.[90]

5. Pre-operative radiotherapy

Due to the liver's poor tolerance to radiation, radiotherapy has had a limited role in the management of CLM. However, better targeting systems such as three-dimensional conformal radiation treatment planning[91] and improved delivery systems such as injectable microspheres have reawakened interest in this modality of treatment.[92] Such forms of therapy are applicable in patients with extensive disease limited to the liver and no extra-hepatic disease. Response rates following selective internal radiation therapy have been reported from 13% to 35% on computed tomography 93.94), although 18F-fluorodeoxyglucose positron tomography suggests a better response rate than the rate of around 70–80%.[94] In spite of these response rates, only one article was found reporting down-staging of CLMs to the point where surgical resection was achievable in 2 of 20 (10%) patients treated with ytrrium-90 microspheres. This particular cohort of patients also received concomitant treatment with oxaliplatin, fluorouracil and leucovorin chemotherapy[95] making interpretation of the efficacy of internal radiotherapy in rendering inoperable CLMs operable problematic.

6. Surgery

Increasing experience and surgical confidence in hepatic resections has led to a radical re-definition of what constitutes inoperable disease. This change in attitude is most marked in radical liver resections pushing the envelope of what is technically possible in patients.

6.1. *Two-stage liver resection*

Two-stage hepatectomy has been proposed for patients with bi-lobar disease, whereby the volume of liver requir-

Table 3 – Survival following surgical resection of CLM made resectable after down-staging with hepatic arterial infusion chemotherapy

Study	Year	Number of patients	Regimen	Additional intervention	Response rate	Resection rate	Median survival (months)	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Iguchi et al.[87]	2008	21	5-FU	–	–	–	386 d	–	–	–	–
Del Freo et al.[a 88]	2006	21	Oxaliplatin and 5-FU	–	5% complete response 19% partial response	9.5	–	–	–	–	–
Selzner et al.[89]	2006	11	Flouridine	Portal vein ligation	–	54.5	20	–	–	–	–
Miyanari et al.[90]	2002	64	Flouridine	–	–	25	–	–	–	–	35.1
Clavien et al.[91]	2002	23	Flurodeoxyuridine	–	40%	26	100	–	–	50	–
Meric et al.[92]	2000	383	5-FU or Flurodeoxyuridine and leucovorin/mitomycin	RFA	–	4.4	9_{DF}	83	–	–	–
Link et al.[93]	1999	74	5-FU ± mitomycin	–	–	12	–	–	–	–	–
Elias et al.[94]	1995	196	5-FU, mitomycin C or 5-FU-priubicin	Portal vein embolisation	–	4.6	–	–	–	–	55.6

RFA = Radiofrequency ablation.
DF = Disease free.
a Pre-treated with systemic chemotherapy.

Table 4 – Results following two-stage hepatectomy for colorectal liver metastases

Study	Year	Number of patients	Additional intervention	Mortality (%)	Percentage undergoing second resection	Follow-up (months)	Median survival (months)	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Chun et al.[102]	2007	21	PVE	0	–	25	–	95 70_{DF}	–	86 51_{DF}	–
Lygidakis et al.[103]	2007	32	PVE, MWA & HAI	–	–	31	28[a]	100	–	80	–
Togo et al.[104]	2005	11	–	0	–	–	18	90	–	45	–
Jaeck et al.[105]	2004	33	PVE and RFA	0	75.7	–	–	70	–	54.4	–
Garcea et al.[106]	2004	11	–	0	90.9	13	17[a]	–	–	–	–
Shimada et al.[107]	2004	12	PVE	0	–	–	–	–	–	–	–
Adam et al.[108]	2000	16	–	0	81	–	31	–	–	35	–

PVE = Portal vein embolisation/ligation.
DF = Disease free.
MWA = Microwave ablation (bridging measure for tumours left in).
HAI = Hepatic intra-arterial chemotherapy.
RFA = Radiofrequency Ablation.
a Mean survival.

ing resection to clear all disease would impinge on remnant liver function. Due to the liver's ability to regenerate, it is possible to resect or 'clear' one lobe of the liver, followed by a second procedure to resect the remaining metastases once the liver has regenerated. There is evidence that two-stage hepatectomy preserves more functioning liver than a one-stage hepatectomy with pre-operative portal vein embolisation.[96] A major problem encountered with this approach is disease progression whilst awaiting second resection. Progression rates have been reported as being as high as 46.7% (from a series including a range of tumours including hepatocellular carcinoma),[97] although most studies report second hepatectomy rates of between 80% and 90% (Table 4).[98–104] For those patients achieving a second resection, 3-year survival rates are good at 35–86% (Table 4).

Two-stage hepatectomy is often provided with a number of other therapeutic interventions including portal vein embolisation (in an attempt to suppress tumour growth in the lobe with remaining metastases whilst stimulating growth in the operated lobe)[98,99,101,103] or ablation of remaining lesions to control tumour growth in the liver remnant as a bridging measure to second hepatectomy.[99,101] All studies examined employed either systemic or regional chemotherapy, in addition to surgery. Technical considerations in undertaking two-stage resections include whether to take the larger volume of liver at first hepatectomy or undertake the smaller resection first. Approaches vary form centre to centre. The authors approach is to undertake the lesser resection first since it has been shown that liver regeneration can stimulate tumour metastases growth.[105]

6.2. *Tumours invading the inferior vena cava*

It was previously considered that involvement of the inferior vena cava (IVC) by a tumour was a contraindication to resection. However, techniques such as total vascular exclusion of the liver has enabled resection of CLMs combined with resection of the IVC, with an acceptable mortality of between 4% and 11% and 5-year survival of up to 38.3%.[106–109] However, survival data for these series are confounded by the inclusion of all types of liver tumours and not just CLMs. IVC resection can be considered, provided there is a good expectation of an R0 resection and suitable expertise exists at the treating centre. However, only a select number of patents would be suitable for this procedure.

6.3. *Ex vivo* liver resection

Ex vivo liver resection refers to the removal of liver from its anatomical attachments, vascular inflow and drainage followed by resection of the target lesion. The liver is then auto-transplanted back into the patient.[110–112] A modification of this technique involves complete mobilisation and exteriorisation of the liver without transection of the hepatic pedicle.[113] The increased exposure and bloodless field, thus created, allows for the resection of awkwardly placed and large hepatic lesions. *Ex vivo* liver resection has frequently been utilised in resection of liver tumours involving the IVC with a reported mortality of 9–25% in more recent reports.[107,114] No large-scale data on survival following this

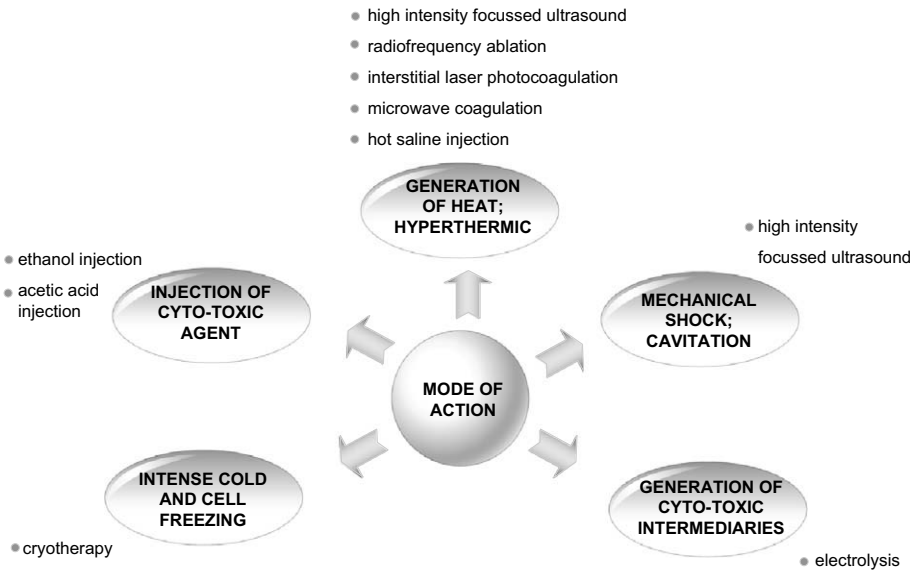

Fig. 1 – Main focal liver ablative techniques, and main mechanism of action.

technique specifically for CLMs exist in the literature. Isolated individual survivals of up to 30 months have been reported.[114] The number of patients who would be eligible for such surgery is few, and at present, *ex vivo* liver resections are performed only in a handful of institutions world-wide.

7. Increasing liver volume

7.1. *Pre-operative portal vein embolisation*

Portal vein embolisation (PVE) involves obliterating portal vein inflow in an attempt to induce atrophy the diseased lobe of the liver with compensatory hypertrophy in the non-diseased side. This can be achieved *via* percutaneous methods under fluoroscopic guidance using materials such as coils, thrombin or gelatine microspheres.[115] Alternative portal vein embolisation may be achieved at laparotomy, such as during as a two-stage hepatectomy, *via* ligature of the appropriate branch of the portal vein.[98] Portal vein embolisation has been shown to increase liver volume by 8–16%, although this increase is dependent on underlying liver function[116–118] and is relatively well tolerated.[117] In the context of this review, PVE is used as part of a multi-disciplinary approach.

8. Ablation

The attraction of focal ablative techniques in patients unsuitable for resection surgery is that they allow the destruction of the tumour deposits whilst preserving as much functional liver tissue as possible. Tumour destruction is achieved by injection of cytotoxic or corrosive agent such as percutaneous ethanol or acetic acid injection (PEI, PAAI); indirect generation of cytotoxic intermediaries such as electrolysis; heating such as radiofrequency ablation (RFA), interstitial laser photocoagulation (ILP), hot saline injection, microwave coagulation therapy (MCT); mechanical shock or cavitation high intensity focused ultrasound (HIFU) or freezing such as cryoablation (Fig. 1). PEI and PAAI have been mainly utilised for the treatment of hepatocellular carcinomas. For this review, the main techniques of ablation used in the management of CLMs clinically will be examined.

8.1. *Radiofrequency ablation (RFA)*

Radiofrequency ablation (RFA) is an electrosurgical technique utilising high frequency alternating current to heat tissues leading to thermal coagulation. When cells are heated above 45 °C, cellular proteins denature and cell membranes lose their integrity as their lipid component melts.[119] It is currently one of the most widely used ablative methods, with more than 80 publications describing the results of RFA in primary liver tumours and colorectal hepatic metastases Percutaneous RFA has been described under general or local anaesthesia,[120,121] along with a laparoscopic approach.[122]

Significant confounding factors in the evaluation of RFA are the short follow-up times and the difficulty in assessing the presence of viable tumour in the surrounding tissue following ablation. Factors which determine survival following RFA include the location of tumours (centrally placed tumours have a higher recurrence), tumour number and tumour size (>4–5 cm). These factors probably relate to the efficacy of achieving complete tumour eradication, if the tumour burden is very high or if the access is technically difficult.[123–126] Analysis of the long-term efficacy of RFA is made difficult by the tendency of studies to report their series incorporating both metastatic lesions and primary hepatocellular cancers together. In addition, early studies in particular tended to report on local recurrence rates, rather than long-term survival following treatment. More recently studies with a longer follow-up have been published revealing 3- and 5-year survival of up to 50% and 30%, respectively, with an acceptable mortality of around 0–2% (Table 5).[123,127–142] One of the largest series of RFA for CLM published in the literature

Table 5 – Outcome after radiofrequency ablation for colorectal hepatic metastases

Study	Year	Tumour size (cm)	Number of patients	Mortality (%)	Median survival (months)	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)	Median follow-up (months)	Local recurrence rate (%)
Siperstein et al.[143]	2007	3.9	235	–	28	–	–	–	18.4	24	–
Abitabile et al.[205]	2007	–	47	0	39	88	80	57	–	33	8.8
Machi et al.[140]	2006	–	100	0	28	90	42	–	30.5	–	–
Suppiah et al.[145]	2007	3.1	30	–	23.2	–	–	–	–	22	–
Navarra et al.[141]	2005	–	38	0	–	72.5	–	52.5	–	18.1	–
Miyamoto et al.[141]	2004	5.2	4	0	–	–	–	–	–	12.7	$n = 1$
Kuvshinoff et al.[127]	2002	4.0	34	0	4_{DF}	–	–	–	–	12	–
Kosari et al.[206]	2002	3.2	18	49% of patients with progressive hepatic disease						19.5	7.7
Ianitti et al.[136]	2002	5.2	52	0	–	–	–	–	–	20.0	–
Elias et al.[135]	2002	2.1	29	–	–	88	55	–	–	14.0	9.0
Machi et al.[207]	2001	3.6	25	1.7	–	–	–	–	–	20.0	8.8
Chung et al.[131]	2001	2.6	6	41% remain free of disease at time of writing; 22% alive with disease; and 37% died with disease						14.0	15.0
De Baere et al.[134]	2000	0.5–4.2	68	–	–	–	–	–	–	13	9
Scudamore et al.[141]	1999	–	10	–	–	–	–	–	–	10	2.2
Pearson et al.[140]	1999	3.6	46	2	–	–	–	–	–	15.0	14.0
Jiao et al.[208]	1999	–	17	–	–	–	–	–	–	10.0	0.0
Cushieri et al.[132]	1999	15.0	8	–	–	–	–	–	–	13.0	1.8
Curley et al.[133]	1999	3.4	61	0	27.6% with disease progression					15.0	5.0
Rossi et al.[147]	1998	2.9	14	–	–	–	–	–	–	10.0	12.0
Lencioni et al.[146]	1998	1.3–5.1	24	–	–	–	–	–	–	6.5	34.0
Solbiati et al.[149]	1997	1.3–5.1	22	–	–	–	–	–	–	12.0	5.0

DF = Disease free.

Table 6 – Outcome after microwave ablation for colorectal hepatic metastases

Authors	Year	Number of patients	Lesion size in cm (mean, range)	% Lesions with complete ablation	Local recurrence (%)	Survival rate (%)				
						1-Year survival	2-Year survival	3-Year survival	4-Year survival	5-Year survival
Kuang et al.[159]	2007	24	2.7	93.2	5.3	–	–	–	–	–
Tanaka et al.[160]	2006	35	0.79	–	37.5	80	–	51	17	–
Liang et al.[161]	2003	149	3.1	–	13.5	91.4	59.5	46.4	29	29
Shibata et al.[a159]	2000	58	4.2	–	–	71	57	14	–	–
Seki et al.[153]	1999	15	2.14	86.7	0	Median survival = 24 months				
Beppu et al.[209]	1998	40	–	80	33	–	–	38	–	33
Matsukawa et al.[163]	1997	7	3.4			83.1	68.7	–	–	–

a Includes resectable lesions.

so far revealed a 5-year of survival of 18.4% using combination RFA and chemotherapy *versus* 0% using chemotherapy alone.[143] These improvements in survival have been helped better radiological imaging techniques which have improved accuracy of localising lesions and in subsequent follow-up to determine local tumour progression. In particular, the advent of combined positron emission tomography and cross-sectional topography (PET/CT) has increased sensitivity for local progression, allowing earlier re-intervention.[144,145]

8.2. *Microwave Ablation (MWA)*

Since its introduction in 1979 by Tabuse,[146] Microwave Coagulation Therapy (MCT) has been used at laparotomy,[146] laparoscopically,[148] percutaneously[149] and thorascopically.[150] MCT is another hyperthermic technique relying on the conversion of energy to heat, to destroy tumours. Larger ablated lesions can also be achieved by selectively blocking the blood flow to the liver.[150–152] Both hepatic artery and venous occlusion result in larger lesion, but venous occlusion appears to have a greater effect on lesion size than arterial occlusion alone.[153] Multiple microwave probes have been used successfully to result in synergistically larger zones of coagulation necrosis.[154] Table 6 summarises the data for microwave ablation and colorectal hepatic metastases, with 3-year survival similar to that achieved with RFA.[119,155–159]

8.3. *Laser Photocoagulation*

Interstitial Laser Photocoagulation (ILP) is another method of causing tissue destruction by heating, thereby inducing coagulative necrosis. ILP was introduced by Bown in 1983 and involves local delivery of laser light *via* the use of flexible fibers. The biological response of tissue following the absorption of laser light results in several different thermal effects. At 40–45 °C, heating and enzyme denaturation occurs. At temperatures of 60–140 °C, cell shrinkage, hyperchromasia, membrane rupture and protein denaturation result. At higher temperatures, from 300 to 1000 °C, vapourisation and carbonisation occur.[160–165]

As with other ablative techniques, long-term survival data are relatively under-reported, with most studies concentrating on short-term survival and local recurrence following ablation (Table 7).[167–178] However, a 5-year survival of up to 30% appears achievable with ILP,[170,171] whilst local recurrence rate would appear to be influenced by tumour size (with larger tumours at increased risk of local recurrence).[170] Major complications are infrequently reported following ILP, although pain and fever are common. Other minor complications are pleural effusion, subcapsular haematoma, paralytic ileus and one case of gastric haemorrhage.[179,180] ILP appears to be a well-tolerated procedure, with a complication rate of approximately 4.7% and mortality rate of 0.3% in over 2,500 ILP procedures.[181]

8.4. *Cryotherapy*

Cryotherapy involves rapid freezing of tissue to sub-zero temperatures which results in ice formation in the extracellular space and cellular damage by dehydration and destruction of normal cellular structures.[182] Ice balls of $4.9 \times 2.2 \times 2.2$ cm

Table 7 – Outcome after interstitial laser photocoagulation for colorectal hepatic metastases

Group and year	Year	Additional procedures	Number of patients	% of Tumours in which full necrosis achieved	Median survival (months)	1-Year survival	2-Year survival	3-Year survival	5-Year survival	Local recurrence rate (%)
Ritz et al.[167]	2007	Microembolisation of Hepatic artery or Pringle	56	–	–	–	–	–	–	Tumour recurrence in 6 patients
Pacella et al.[168]	2006	–	44	61	12.7	–	–	–	–	–
Chrisophi et al.[166]	2004	–	80	–	24.6	–	–	–	3.5%	–
Vogl et al.[a],[170]	2004	–	603	–	3.5 Years	94%	77%	56%	37%	[b]2 cm = 1.9% 2.1–3.0 cm = 2.4% 3.1–4.0 cm = 1.2% >4.0 cm = 4.4%
Vogl et al.[c],[171]	2003	TACE	82	–	26.2	–	–	–	–	–
Vogl et al.[181]	2001	–	376	–	–	63% at 28 months				5.0
Shankar et al.[172]	2000	–	19	–	16	–	–	–	–	–
Gillams and Lees[173]	2000	–	69	–	–				22%	–
Giorgio et al.[180]	2000	–	27	77	–	–	–	–	–	–
Caspani et al.[174]	1997	–	20	77.5	–	–	–	–	–	–
Gillams et al.[175]	1996	–	55	16	–	–	–	–	–	–
Tranberg et al.[176]	1996	–	7	42	–	–	–	–	–	50
Amin et al.[177]	1993	–	22	52	–	–	–	–	–	–
NØlsoe et al.[178]	1993	–	11	75	–	–	–	–	–	36

TACE = Transarterial chemoembolisation.

a Series includes patients unfit for surgery and refusal to undergo surgery, as well as inoperable metastases (18.5% of all patients).

b Tumour size and local recurrence rate.

c Series includes hepatic metastases from other primaries, including breast.

Table 8 – Outcome after cryotherapy for colorectal hepatic metastases

Group	Year	Number of patients	Method of delivery	Median survival (months)	Local recurrence (%)	1 Year (%)	2 Year (%)	3 Year (%)	5 Year (%)
Ruers et al.[184]	2007	45	Laparotomy	31	–	–	56	–	27
Brooks et al.[a185]	2005	86	Laparotomy	–	–	86	–	43	19
Seifert .[b186]	2005	25	Laparotomy	–	–	–	–	–	26
Seifert et al.[b187]	2004	40	Laparotomy	29	20	–	–	44	26
Mala et al.[188]	2004	19	16 Percutaneously 5 Laparotomy 3 Laparoscopically	–	44	–	48	–	–
Yan et al.[a189]	2003	172	Laparotomy	28	–	89	65	41	19
Rivoire et al.[a190]	2002	24	Laparotomy	39	–	94	–	58	37
Seifert et al.[191]	2002	65	Laparotomy	28	20	–	–	38	30
Sheen et al.[192]	2002	57	Laparotomy	22	–	–	–	–	–
Shimonov et al.[193]	2002	10	Laparoscopy	32	–	–	–	–	–
Ruers et al.[194]	2001	30	–	32	–	–	61	–	–
Bilchik et al.[195]	2000	180	–	28	22.8				
Chung et al.[196]	2001	14	Laparotomy	42	–	–	–	–	–
Seifert et al.[197]	2000	49	Laparotomy	29	16	–	–	–	–
Junginer et al.[198]	1998	29	Laparotomy	–	24	–	–	–	–
Weaver et al.[199]	1995	43	Laparotomy	26	–	62	–	–	–
Hewitt et al.[200]	1998	20	Laparotomy	32	35	88	60	_	_

a Cryotherapy combined with liver resection and hepatic artery chemotherapy.
b Cryotherapy combined with liver resection.

can normally be produced with one cryoprobe;[183] however, with the use of multiple probes these ablated lesions can be increased to $6.0 \times 4.9 \times 5.6$ cm.[184]

Interpretation of survival data for cryotherapy is confounded by many studies reporting their survival following a combination and liver resection. However, this probably reflects the evolution of treatment strategies that optimise the options for patients whose CLMs would be inoperable if resection alone was considered. Since cryotherapy has been in wide-spread clinical use for longer than many of

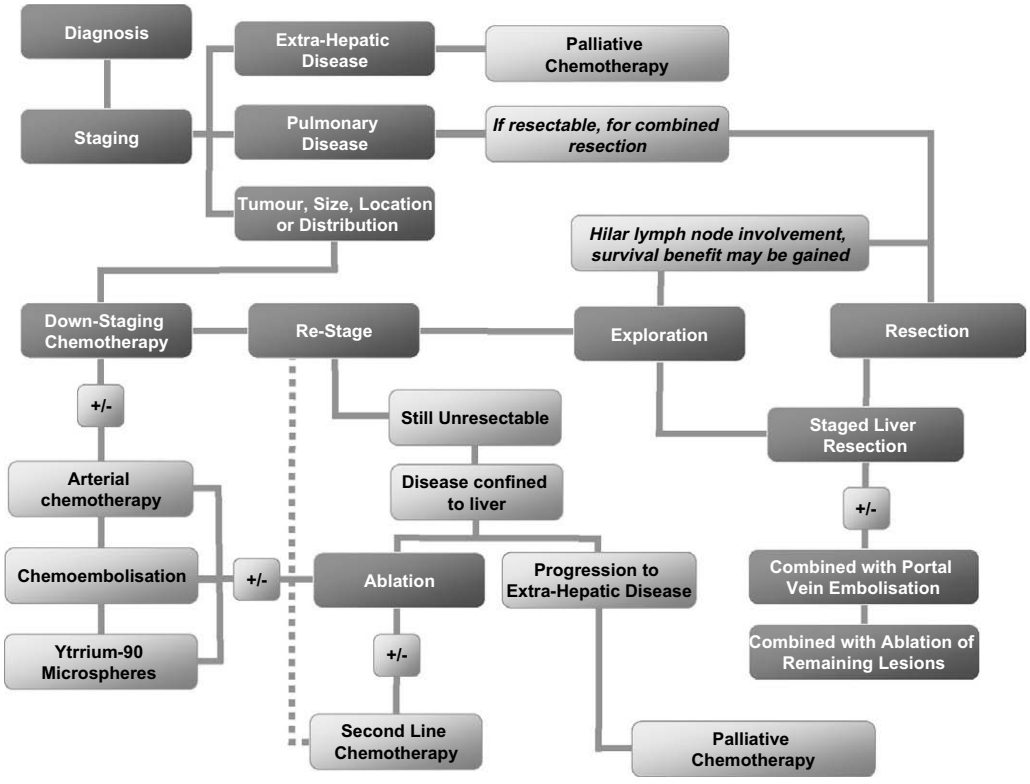

Fig. 2 – Suggested algorithm in the evaluation and treatment options of 'inoperable' liver metastases.

the other ablative methods, there is a greater proportion of long-term survival data in the literature suggesting that survival of up to 30% at 5 years is possible with a combination of chemotherapy, cryotherapy and hepatic resection (Table 8).[184–200]

The overall complication rate following cryotherapy has been reported at 27% with a post-procedure mortality of 0 to 1.4%.[184–200] Haemorrhage may occur following cryotherapy, usually because of cracking of the liver parenchyma during freeze-thaw cycles. This bleeding is exacerbated by the transient thrombocytopenia and coagulopathy following cryotherapy.[201] Perhaps the most feared complication following cryoablation is the phenomenon of cryoshock. This appears to be a systemic inflammatory response that complicates 1% of all cryotherapy procedures with a mortality rate of 18.2%.[202]

No randomised controlled trials exist in the literature comparing ablation therapies with other modalities such as staged resections or systemic chemotherapy alone. A study by Ruers *and colleagues* compared outcomes in three groups of patients; those undergoing radical resection, those who were found at laparotomy to have unresectable disease amenable to ablation and those with unresectable disease unamenable to ablation.[194] As expected, the cohort patients undergoing radical resection had the best survival, but their results suggested that disease-free survival was improved in those undergoing ablation when compared to chemotherapy alone (although the results did not achieve statistical significance) (31 and 26 median survival, respectively), with an improved quality of life.[194] Other experimental technologies are currently under evaluation, such as electrolysis which are not reliant on heat or cavitation-induced tissue destruction, but rather on free-radical formation.[203]

The main limitation to all ablative methods discussed is a loss in efficacy for larger tumours and near major portal or biliary structures. The "heat-sink" effect caused by flow within these major vessels results in a loss in tumour-killing capability and, in addition, ablation near these areas may also carry risk the injury to the vessels themselves. Many CLMs, as discussed in the intervening paragraphs, are frequently conventionally inoperable as a combination of size and location. Hence, the role of ablation would have to be considered a second choice to attempted resection.

9. Conclusion

Although promising, there are currently a bewildering number of therapeutic options available for patients with seemingly inoperable CLMs. These various treatments frequently overlap the boundaries of specialities and highlight the need for careful evaluation of such patients at multi-disciplinary teams. Similar 5-year survivals are evident across the varying modalities of therapy reviewed; however, the underlying disease burdens in these patients are not directly comparable. It would seem that down staging to resection should be the main goal of treatment, since this strategy carries with it the potential for cure. The possibility of a stage liver resection should be considered, and this can be combined with portal vein embolisation or ablation of lesions in remaining segments of the liver as a "bridge" to the second resection (Fig. 2). However, flexibility is essential and combinations of different treatments should be also considered. A nihilistic approach should be avoided at all costs and all surgeons treating these individuals must keep up-to-date with the current literature reporting on outcomes following such multimodality therapy.

Conflict of interest statement

None declared.

REFERENCES

1. Geoghan JG, Scheele J. Treatment of colorectal of liver metastases. *Br J Surg* 1999;**86**:158–69.
2. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;**13**:1271–80.
3. Fegiz G, Ramacciato G, Gennari L, et al. Hepatic resections for colorectal metastases: the Italian experience. *J Surg Oncol Suppl* 1991;**2**:144–54.
4. Meijer S, Paul MA, Cuesta MA, Blomjous J. Intra-operative ultrasound in detection of liver metastases. *Eur J Cancer* 1995;**31A**:1210–1.
5. Scheele J, Stang R, Altendorf-Hofmann A, Paul MA. Resection of colorectal liver metastases. *W J Surg* 1995;**19**:59–71.
6. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. *Br J Surg* 1986;**73**:732–5.
7. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer. A comparison with resective treatment.. *Ann Surg* 1984;**199**:502–8.
8. Furhman GM, Curley SA, Hohn DC, Roh MS. Improved survival after resection of colorectal liver metastases. *Ann Surg Oncol* 1995;**2**:537–41.
9. Gayowski TJ, Iwatsuki S, Madariaga JR, et al. Experience in hepatic resection for metastatic colorectal cancer: analysis of clinical and pathologic risk factors. *Surgery* 1994;**116**:703–10.
10. Taylor M, Forster J, Langer B, Taylor BR, Greig PD, Mahut C. A study of prognostic factors for hepatic resection for colorectal metastases. *Am J Surg* 1997;**173**:467–71.
11. Nagashima I, Oka T, Hamda C, Naruse K, Osada T, Muto T. Histopathological prognostic factors influencing long-term prognosis after surgical resection for hepatic metastases from colorectal cancer. *Am J Gastroenterol* 1999;**94**:739–43.
12. Yamamoto J, Shimada K, Kosuge T, Yamasaki S, Sakamoto M, Fukuda H. Factors influencing survival of patients undergoing hepatectomy for colorectal metatases. *Br J Surg* 1999;**86**:332–7.
13. Scheele J, Stangle R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990;**77**:1241–6.
14. Garden OJ, Rees M, Poston GJ, et al. Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006;**55**:iii1–8.
15. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *The Oncologist* 2008;**13**:51–64.
16. Ekberg H, Tranberg KG, Andersson R, et al. Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986;**73**:727–31.
17. Cady B, Jenkins RL, Steele GD, et al. Surgical margin in hepatic resection for colorectal metastasis: a critical and

improvable determinant of outcome. *Ann Surg* 1998;**227**:566–71.
18. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;**241**:634–5.
19. Bodingbauer M, Tamandl D, Schmid K, Plank C, Schima W, Gruenberger T. Size of surgical margin does not influence recurrence rates after curative resection liver resection for colorectal cancer liver metastases. *Br J Surg* 2007;**94**:1133–338.
20. Mann CD, Metcalfe MS, Leopardi LN, Maddern GJ. The clinical risk score: emerging as a reliable preoperative prognostic index in hepatectomy for colorectal metastases. *Arch Surg* 2004;**139**:1168–72.
21. Mala T, Bohler G, Mathisen O, Bergan A, Soreide O. Hepatic resection for colorectal metastases: can preoperative scoring predict patient outcome? *W J Surg* 2002;**26**:1348–53.
22. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence for hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;**230**:309–18.
23. Pawlik TM, Abdalla EK, Ellis LM, Vauthey JN, Curley SA. Debunking dogma: surgery for four or more colorectal liver metastases is justified. *J Gastrointes Surg* 2006;**10**:240–8.
24. Chun YS, Vauthey JN. Extending the frontiers of resectability in advanced colorectal cancer. *Eur J Surg Oncol* 2007;**33**:S52–8.
25. Pederson IK, Burcharth F, Roikjaer O, Bader H. Resection of liver metastases from colorectal cancer. *Indications and results. Dis Colon Rectum* 1994;**37**:1078–82.
26. Hamady ZZ, Malik HZ, Finch R. Hepatic resection for colorectal metastasis: impact on tumour size. *Ann Surg Oncol* 1992;**216**:715–22.
27. Warwick R, Page R. Resection of pulmonary metastases from colorectal carcinoma. *Eur J Surg Oncol* 2007;**33**:59–63.
28. Iizasa T, Suzuki M, Yoshida J, et al. Prediction of prognosis and surgical indications for pulmonary metastectomy from colorectal cancer. *Ann Thorac Surg* 2006;**82**:254–60.
29. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Intl J Colorect Dis* 2007;**22**:699–704.
30. Inoue M, Ohta M, Iuchi K, et al. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2005;**78**:238–44.
31. Nakajima J, Murakawa T, Fukami T, Takamoto S. Is thorascopic surgery justified to treat pulmonary metastasis from colorectal cancer? *Interact Cardiovasc Thorac Surg* 2008;**7**:212–6.
32. Welter S, Jacobs J, Krbek T, Krebs B, Stamatis G. Long-term cancer survival after repeated resection of pulmonary metastases from colorectal cancer. *AnnThorac Surg* 2007;**84**:203–10.
33. Smith JW, Fortner J, Burt M. Resection of hepatic and pulmonary metastases from colorectal cancer. *Surg Oncol* 1992;**16**:399–404.
34. Headrich JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001;**71**:975–9.
35. Hamy A, Baron O, Bennouna J, Roussel JC, Paineau J, Douillard JY. Resection of hepatic and pulmonary metastases in patients with colorectal cancer. *Am J Clin Oncol* 2001;**24**:607–9.
36. Nagakura S, Shirai Y, Yamoto N, Suda T, Hatakeyama K. Simultaneous detection of colorectal carcinoma liver and lung metastases does not warrant resection. *J Am Coll Surg* 2001;**193**:153–60.
37. Joosten J, Bertholet J, Keemers-Gels M, Barendregt W, Ruers T. Pulmonary resection of colorectal metastases in patients with or without a history of hepatic metastases. *Eur J Surg Oncol* 2008;**34**:895–99.
38. Lee WS, Yun HR, Yun SH, et al. Treatment outcomes of hepatic and pulmonary metastases from colorectal carcinoma. *J Gastroenterol Hepatol* 2007;Dec 14 [Epub ahead of print].
39. Miller G, Biernacki P, Kemeny NE, et al. Outcomes after resection of synchronous or metachronous hepatic and pulmonary colorectal metastases. *J Am Coll Surg* 2007;**205**:231–8.
40. Takahashi S, Nagai K, Saito N, et al. Multiple resections for hepatic and pulmonary metastases of colorectal carcinoma. *Jap J Clin Oncol* 2007;**37**:186–92.
41. Reddy RH, Kumar B, Mirsadraee S, Papgiannopoulos K, Lodge P, Thorpe JA. Staged pulmonary and hepatic metastasectomy in colorectal cancer: is it worth it? *Eur J Cardiothorac Surg* 2004;**25**:151–4.
42. Lee WS, Kim J, Yun HR, Chun HK, Lee WS, Kim Y. Risk factor stratification after simultaneous liver and colorectal resection for synchronous colorectal metastases. *Lang Arch Surg* 2008;**393**:13–9.
43. Shah SA, Haddad R, Al-Sukhni W, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. *J Am Coll Surg* 2006;**202**:468–75.
44. Patel NA, Keenan RJ, Meich DS, et al. The presence of colorectal hepatic metastases does not preclude pulmonary metastectomy. *Am Surg* 2003;**69**:1047–53.
45. Vogelsang H, Haas S, Hierholzer C. Factors influencing survival after resection of pulmonary metastases from colorectal cancer. *Br J Surg* 2004;**91**:1066–71.
46. Kanemitsu Y, Kato T, Hirai T. Preoperative probability model for predicting overall survival after resection of pulmonary metastases from colorectal cancer. *Br J Surg* 2004;**91**: 112–20.
47. Saito N, Omiya H, Kohno K, et al. Pulmonary metastectomy for 165 patients with colorectal carcinoma: a prognostic assessment. *J Thorac Cardiovas Surg* 2002;**124**:1007–10013.
48. Yang YL, Fleshman JW, Strasberg SM. Detection and management of extrahepatic colorectal cancer in patients with resectable liver metastases. *J Gastrointest Surg* 2007;**11**:929–44.
49. Jaeck D, Nakano H, Bachellier P, et al. Significance of hepatic pedicle lymph node involvement in patients with colorectal liver metastases: a prospective study. *Ann Surg Oncol* 2002;**9**:430–8.
50. Bennett JJ, Scmidt CR, Klimstra DS, et al. Perihepatic lymph node micrometastases impact outcome after partial hepatectomy for colorectal metastases. *Ann Surg Oncol* 2008;**15**:1130–6.
51. Korita PV, Wakai T, Sakata J, et al. Intrahepatic lymphatic invasion predicts poor survival and recurrences after hepatectomy in patients with colorectal carcinoma metastases. *Ann Surg Oncol* 2007;**14**:3472–80.
52. Laruent C, Cunha A, Rullier E, Smith D, Sarie J. Impact of microscopic hepatic lymph node involvement on survival after resection of colorectal liver metastases. *J Am Coll Surg* 2004;**198**:884–991.
53. Rodgers MS, McCall JL. Surgery for colorectal liver metastases with hepatic lymph node involvement: a systematic review. *Br J Surg* 2000;**87**:1142–55.
54. Dworkin MJ, Earlam S, Fordy C, Allen-Mersh TG. Importance of hepatic artery node involvement in patients with colorectal liver metastases. *J Clin Pathol* 1995;**48**:270–2.
55. Jaeck D. The significance of hepatic pedicle lymph node metastases in surgical management of colorectal liver metastases and of other liver malignancies. *Ann Surg Oncol* 2003;**10**:1007–11.

56. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;**21**:3737–43.
57. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable their localisation does not matter but their total number has a prognostic effect. *Ann Surg Oncol* 2005;**12**:900–9.
58. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer. *J Clin Oncol* 2004;**22**:3284–92.
59. Schrag D, Wesier M, Schattner M. An increasingly common challenge: management of the complete responder with multi-focal metastatic colorectal cancer. *J Clin Oncol* 2005;**23**:1799–802.
60. Elias D, Youssef O, Sideris L. Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. *J Surg Oncol* 2004;**86**:4–9.
61. Bertheault-Cvitkovic F, Jami A, Ithzaki M, et al. Biweekly intensified ambulatory chronomodulated chemotherapy with oxaliplatin, fluorouracil and leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol* 1996;**14**:2950–8.
62. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;**18**:2938–47.
63. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2000;**25**:1041–7.
64. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin and irinotecan (FOXFOXIRI) compared with infusion fluorouracil, leucovorin and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologicao Nord Ovest. *J Clin Oncol* 2007;**26**:1670–6.
65. Kohne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer. *European Organisation for Research and Treatment of Cancer Gastrointestinal Group 40986. J Clin Oncol* 2005;**23**:4856–65.
66. Levi F, Misset JL, Brienza S, et al. A chronopharmacologic phase II clinical trial with 5-fluorouracil and oxaliplatin using an ambulatory multichannel programmable pump. *High antitumour effectiveness against colorectal cancer. Cancer* 1992;**69**:893–900.
67. Levi F, Zidani R, Misset JL. Randomized multicentre trial of chronotherapy with oxaliplatin, fluorouracil and folinic acid in metastatic colorectal cancer. *International Centre for Cancer Chronotherapy. Lancet* 1997;**350**:681–6.
68. Ho WM, Ma B, Mok T, et al. Liver resection after irinotecan, 5-fluorouracil and folinic acid for patients with unresectable colorectal liver metastases: a multi-centre phase II study by the Cancer Therapeutic Research Group. *Med Oncol* 2005;**22**:303–12.
69. Alberts SR, Horvath W, Sternfeld WC. Oxaliplatin, fluorouracil and leucovorin for patients with unresectable liver only metastases from colorectal cancer: a North Central Treatment Group Phase II study. *J Clin Oncol* 2005;**23**:9243–9.
70. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer. *Ann Oncol* 2004;**15**:933–9.
71. Giacchetti S, Itzhaki M, Gruia G, et al. Long-term survival of patients with unresectable colorectal cancer liver metastases following infusional chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and surgery. *Ann Oncol* 1999;**10**:663–9.
72. Masi G, Cupini S, Marcucci L, et al. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. *Ann Surg Oncol* 2006;**13**:58–65.
73. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy. *Ann Surg* 2004;**4**:644–58.
74. Adam R, Avisar E, Ariche A. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal cancer. *Ann Surg Oncol* 2001;**8**:347–53.
75. Bismuth H, Adam R, Levi F, et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 1996;**4**:509–22.
76. Folwer WC, Eisenberg BL, Hoffman JP. Hepatic resection following systemic chemotherapy for metastatic colorectal carcinoma. *J Surg Oncol* 1992;**51**:122–5.
77. Folprecht G, Lutz MP, Schoffski P, et al. Cetuximab and irnotecan/5-fluorouracil/folinic acid is a safe combination for first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal carcinoma. *Ann Oncol* 2006;**17**:450–6.
78. Adam R, Aloia T, Levi F, et al. Hepatic resection after cetuximab treatment for colorectal liver metastases previously refractory to conventional systemic chemotherapy. *J Clin Oncol* 2007;**25**:4593–602.
79. Shaw RJ, Cantley LC. Ras, PI(3)k and mTOR signaling controls tumour cell growth. *Nature* 2006;**441**:424–30.
80. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Can Res* 2007;**67**:2643–8.
81. Hurwitz H, Fehrenbacher L, Novotny W. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Eng J Med* 2004;**350**:2335–42.
82. Kopetz S, Abbruzzese Jl, Eng C. Preliminary results from a phase II study of infusional 5-FU, leucovorin, and irinotecan (FOLFIRI) plus bevacizumab as first-line treatment for metastatic colorectal cancer. *J Clin Oncol* 2006. Abstract 3579.
83. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab capecitabine and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. J Clin Oncol;26:1830-1835.
84. D'Angelica M, Kornprat P, Gonen M, et al. Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. *Ann Surg Oncol* 2007;**14**:759–65.
85. Chang AE DSP, Surgarbaker PH, Simpson C, Culnanen M, Steinberg SM. A prospective randomized trial of regional versus systemic continuous 5-fluourdexoyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987;**206**:685–93.
86. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery flouridine infusion for colorectal liver metastases. *Lancet* 1994;**344**:1255–60.
87. Iguchi T, Arai Y, Inaba Y, et al. Hepatic arterial infusion chemotherapy through a port-catheter system as preoperative initial therapy in patients with advanced liver dysfunction due to synchronous and unresectable liver

metastases from colorectal cancer. *Cardiovasc Intervent Radiol* 2008;**31**:86–90.
88. Del Freo A, Fiorentini G, Sanguinetti F, et al. Hepatic arterial chemotherapy with oxaliplatin, folinic acid and 5-fluorouracil in pre-treated patients with liver metastases from colorectal cancer. *In Vivo* 2006;**20**:743–6.
89. Selzner N, Pestalozzi BC, Kadry Z, Selzner M, Wildermuth S, Clavien PA. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. *Br J Surg* 2006;**93**:587–92.
90. Miyanari N, Mori T, Takahashi K, Yasuno M. Evaluation of aggressively treated patients with unresectable multiple liver metastases from colorectal cancer. *Dis Colon Rectum* 2002;**45**:1503–9.
91. Clavien PA, Selzner M, Morse M, Selzner M, Paulson E. Downstaging of hepatocellular carcinoma and liver metastases from colorectal cancer by selective intra-arterial chemotherapy. *Surgery* 2002;**131**:433–42.
92. Meric F, Yehuda Z, Patt MD, et al. Surgery after downstaging of unresectable hepatic tumours with intra-arterial chemotherapy. *J Surg Oncol* 2000;**7**:490–5.
93. Link KH, Pillarsch J, Formetinin A, et al. Downstaging by regional chemotherapy of non-resectable isolated colorectal liver metastases. *Eur J Surg Oncol* 1999;**25**:381–8.
94. Elias D, Lasser P, Rougier P, Ducreux M, Bognel C, Rochel A. Frequency, technical aspects results and indications of major hepatectomy after prolonged intra-arterial chemotherapy for initially unresectable hepatic tumours. *J Am Coll Surg* 1995;**180**:213–9.
95. Dawson LA, McGinn CJ, Lawrence TS. Conformal chemoradiation for primary and metastatic liver malignancies. *Sem Surg Oncol* 2003;**21**:249–55.
96. Ho S, Lau WY, Leung TWT, Johnson PJ. Internal radiation therapy for patients with primary or metastatic hepatic cancer. *Cancer* 1998;**83**:1894–907.
97. Jiao LR, Szysko T, Al-Nahhas A, et al. Clinical and imaging experience with yttrium-90 spheres in the management of unresectable liver tumours. *Eur J Surg Oncol* 2007;**33**:597–602.
98. Lewandoswki RJ, Thurston KG, Goin JE, et al. 90Y microsphere (TheraSphere) treatment for unresectable colorectal cancer metastases of the liver: response to treatment at targeted doses of 135–150 Gy as measured by [18F] fluorodeoxyglucose positron tomography and computed tomographic imaging. *J Vasc Intervention Radiol* 2005;**16**:1641–51.
99. Sharma RA, Van Hazel GA, Morgan B, et al. Radioembolization of liver metastases from colorectal cancer using yttrium-90 microspheres with concomitant systemic oxaliplatin, fluorouracil and leucovorin chemotherapy. *J Clin Oncol* 2007;**25**:1099–106.
100. Tanaka K, Shimada H, Matsuo K, Ueda M, Endo I, Togo S. Remnant liver regeneration after two-stage hepatectomy for multiple bilobar colorectal metastases. *Eur J Surg Oncol* 2007;**33**:329–35.
101. Popescu I, David L, Brasoveanu V, Boros M, Hrehoret D. Two-stage hepatectomy: an analysis of a single center's experience. *Magy Seb* 2006;**59**:184–9.
102. Chun YS, Vauthey JN, Ribero D, et al. Systemic chemotherapy and two-stage hepatectomy for extensive bi-lateral colorectal liver metastases: perioperative safety and survival. *J Gastrointest Surg* 2007;**11**:498–504.
103. Lygidakis NJ, Bhagat AD, Vrachnos P, Grigorakakos L. Challenges in everyday surgical practice. a synchronous bilobar hepatic colorectal metastases: newer multimodality approach. *Hepatogastroenterol* 2007;**54**:1020–4.
104. Togo S, Nagano K, Masui H, et al. Two-stage hepatectomy for multiple bilobular liver metastases from colorectal cancer. *Hepatogastroenterol* 2005;**52**:913–9.
105. Jaeck D, Oussoultzolgou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolisation to achieve curative resection for initially unresectable multiple and bi-lobar liver metastases. *Ann Surg* 2004;**240**:1037–9.
106. Garcea G, Polemonivi N, Lloyd TD, Steward WP, Dennison AR, Berry DP. Two-stage liver resection and chemotherapy for bilobar colorectal liver metastases. *Eur J Surg Oncol* 2004;**30**:759–64.
107. Shimada H, Tanaka K, Masui H, et al. Results of surgical treatment for multiple (>= 5 nodules) bi-lobar hepatic metastases from colorectal cancer. *Lang Arch Surg* 2004;**389**:114–21.
108. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. Two-stage hepatectomy: a planned strategy to treat unresectable liver tumours. *Ann Surg* 2000;**232**:777–85.
109. Harun N, Nikarjam M, Muralidharan V, Christophi C. Liver regeneration stimulates tumour metastases. *J Surg Res* 2007;**138**:284–90.
110. Arii S, Teramoto K, Kawamura T, et al. Significance of hepatic resection combined with inferior ven cava resection and its reconstruction with expanded polytetrafluoroethylene for the treatment of liver tumours. *J Am Coll Surg* 2003;**196**:243–9.
111. Hemming AW, Reed AI, Langham MR, Fujita S, Howard RJ. Combined resection of the liver and inferior vena cava for hepatic malignancy. *Ann Surg* 2004;**239**:712–9.
112. Madariaga JR, Fung J, Gutierrez J, Bueno J, Iwatshuki S. Liver resection combined with excision of vena cava. *J Am Coll Surg* 2000;**191**:244–50.
113. Azoulay D, Andreanni P, Maggi U. Combined liver resection and reconstruction of the supra-renal vena cava: The Paul Brousse experience. *Ann Surg* 2006;**244**:80–8.
114. Forni E, Meriggi F. Bench surgery and liver autotransplantation. Personal experience and technical considerations. *G Chir* 1995;**16**:407–13.
115. Yanaga K, Kishikawa K, Shimada H, et al. Extracorporeal hepatic resection for previously unresectable neoplasms. *Surgery* 1993;**113**:636–43.
116. Pichlmayr R, Grosse H, Hausse J, Gubernatis G, Lamesch P, Breschneider HJ. Technique and preliminary results of extracorporeal liver surgery (bench procedure) and surgery on the in situ perfused liver. *Lancet* 1990;**77**:21–6.
117. Hannoun T, Borie D, Balladur P, et al. Ex situ-in-vivo hepatic resection. Technique and results. *Chirugie* 1992;**118**:292–6.
118. Lodge P, Ammori BJ, Prasad K, Bellamy MC. Ex vivo and in situ resection of the inferior vena cava with hepatectomy for colorectal metastases. *Ann Surg* 2000;**231**:471–9.
119. Wicherts DA, Haas S, Adam R. Bringing unresectable disease to resection with curative intent. *Eur J Surg Oncol* 2007;**33**:S42–51.
120. Farges O, Belghiti J, Kianmanesh R. Portal vein embolisation before right hepatectomy: prospective clinical trial. *Ann Surg* 2003;**237**:208–17.
121. Madoff DC, Hicks ME, Abdalla EK. Portal vein embolisation with polyvinyl alcohol particles and coils in preparation for major liver resection for hepatobiliary malignancy Safety and effectiveness: study in 26 patients. *Radiology* 2003;**227**:251–60.
122. Vauthey JN, Cahaui A, Do KA. Standardized measurement of the future liver remnant prior to extended liver resection. *Methodology and clinical associations. Surgery* 2000;**127**:512–9.
123. Lounsberry WG V, Linke C. The early histological changes following electrocoagulaton. *Gastrointest Endosc* 1995;**41**:60–8.
124. Livraghi T, Goldberg SN, Monti F, et al. Saline-enhanced radio-frequency tissue ablation in the treatment of liver metastases. *Radiology* 1997;**202**(1):205–10.

125. Solbiati L, Lerace T, Goldberg SN, et al. Percutaneous US-guided radio-frequency tissue ablation of liver metastases: treatment and follow-up in 16 patients. *Radiology* 1997;**202**(1):195–203.
126. Buscarini L, Rossi S, Fornari F, Di Stasi M, Buscarini E. Laparoscopic ablation of liver adenoma by radiofrequency electrocautery. *Gastrointest Endosc* 1995;**41**(1):68–70.
127. Kuvshinoff BW, Ota DM. Radiofrequency ablation of liver tumours; influence of technique and tumours size. *Surgery* 2002;**132**:605–12.
128. Yu H, Cheng J, Lai K, et al. Factors for early tumor recurrence of single small hepatocellular carcinoma after percutaneous radiofrequency ablation therapy. *W J Gastroenterol* 2005;**11**:1439–44.
129. Berber E, Pelly R, Siperstein A. Predictors of survival after radiofrequency thermal ablation of colorectal cancer metastases to the liver; a prospective study. *J Clin Oncol* 2005;**23**:1358–64.
130. Choy P, Koea J, McCall J, Holden A, Osbourne M. The role of radiofrequency ablation in the treatment of primary and metastatic tumors of the liver: initial lessons learned. *N Z Med J* 2002;**115**(1159):U128.
131. Chung M, Wood TF, Tsioulias GJ. Laparoscopic radiofrequency ablation of unresectable hepatic malignancies: a phase II trial.. *Surg Endosc* 2001;**15**:1020–6.
132. Curley SA, Izzo F, Delrio P. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Am Surg* 1999;**230**:1–8.
133. Cuschieri A, Bracken J, Boni L. Initial experience with laparoscopic ultrasound-guided radiofrequency thermal ablation of hepatic tumours. *Endoscopy* 1999;**31**:318–21.
134. De Baere T, Elias D, Dromain C, et al. Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. *Am J Roentgenol* 2000;**175**:1619–25.
135. Elias D, De Baere T, Smayra T. Al. *E. Percutaneous radiofrequency thermoablation as an alternative to surgery for the treatment of liver tumour recurrence after hepatectomy. Br J Surg* 2002;**89**:752–6.
136. Iannitti DA, Dupuy DE, Mayo-Smith WW, Murphy B. Hepatic radiofrequency ablation. *Arch Surg* 2002;**137**:422–7.
137. Machi J, Oishi AJ, Sumida K, et al. Long-term outcome of radiofrequency ablation for unresectable liver metastases from colorectal cancer: evaluation of prognostic factors and effectiveness in first and second-line management. *Can J* 2006;**12**:318–26.
138. Miyamoto N, Tsuji K, Sakurai Y, et al. Percutaneous radiofrequency ablation for unresectable large hepatic tumours during hepatic blood flow occlusion in four patients. *Clin Radiol* 2004;**59**:812–8.
139. Navarra G, Ayav A, Weber JC, et al. Short and long-term results of intraoperative radiofrequency ablation of liver metastases. *Intl J Colorect Dis* 2005:20.
140. Pearson AS, Izzo F, Fleming RY. Intraoperative radiofrequency ablation or cryoablation for hepatic malignancies. *Am J Surg* 1999;**178**:592–9.
141. Scudamore CH, Lee SI, Patterson EJ. Radiofrequency ablation followed by resection of malignant liver tumours. *Am J Surg* 1999;**177**:411–7.
142. Suppiah A, White TJ, Roy-Choudhury SH, et al. Long-term results of percutaneous radiotherapy ablation of unresectable colorectal hepatic metastases: final outcome. *Dig Surg* 2007;**24**:358–60.
143. Siperstein AE, Berber E, Ballem N, Parikh RT. Survival after radiofrequency ablation of colorectal liver metastases: 10 year experience. *Ann Surg* 2007;**246**:559–67.
144. Keuhl H, Antoch G, Sergar H, Veit-Haibach P, Rosenbaum-Krumme S, Vogt F, Frilling A, Barkhuesen J, Bockish A. Comparison of FDG-PET, PET/CT and MRI for follow-up of colorectal liver metastase treated with radiofrequency ablation; initial results. *Eur J Radiol*, 2008;**62**:362–71.
145. Kuehl H, Stattus J, Hertel S, Hunold P, Kaiser G, Bocksih A, et al. Mid-term outcome of positron emission tomography/computed tomography-assisted radiofrequency ablation in primary and secondary liver tumours: a single-centre experience. *Clin Oncol* 2008;**20**:234–40.
146. Lencioni R, Goletti O, Armillota N. Radiofrequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. *Eur Radiol* 1998;**8**:1205–11.
147. Rossi S, Di Stasi M, Buscarini E. Interstitial thermal ablation in the treatment of hepatic cancer. *Am J Roentgenol* 1996;**167**:759–68.
148. Rossi S, Stasi M, Buscarini E. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am* 1995;**1**:73–7.
149. Solbiati L, Goldberg S, Ierace T. Hepatic metastases: percutaneous radiofrequency ablation with cooled-trip electrodes. *Radiology* 1997;**205**:367–73.
150. Tabuse K. A new operative procedure of hepatic surgery using a microwave tissue coagulator. *Nipp Geka Hokan* 1979;**48**(2):160–72.
151. Tabuse K, Katsumi M. Application of a microwave tissue coagulator to hepatic surgery the haemostatic effects on spontaneous rupture of hepatoma and tumor necrosis. *Nipp Geka Hokan* 1981;**50**(4):571–9.
152. Watanabe Y, Sato M, Abe Y, et al. Laparoscopic microwave coagulo-necrotic therapy for hepatocellular carcinoma: a feasible study of an alternative option for poor-risk patients. *J Laparoendosc Surg* 1995;**5**(3):169–75.
153. Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994;**74**(3):817–25.
154. Shimada S, Hirota M, Beppu T, et al. Complications and management of microwave coagulation therapy for primary and metastatic liver tumors. *Surg Today* 1998;**28**(11):1130–7.
155. Takamura M, Murakami T, Shibata T, et al. Microwave coagulation therapy with interruption of hepatic blood in- or outflow: an experimental study. *J Vasc Interv Radiol* 2001;**12**(5):619–22.
156. Ishida T, Murakami T, Shibata T, et al. Percutaneous microwave tumor coagulation for hepatocellular carcinomas with interruption of segmental hepatic blood flow. *J Vasc Interv Radiol* 2002;**13**(2 pt 1):185–91.
157. Shibata T, Morita T, Okuyama M, Kitada M, Shimano T, Ishida T. Comparison of percutaneous microwave coagulation area under interruption of hepatic arterial blood flow with that under hepatic arterial and venous blood flow for hepatocellular carcinoma. *Gan To Kagaku Ryoho* 2002;**29**(12):2146–8.
158. Wright AS, Lee Jr FT, Mahvi DM. Hepatic microwave ablation with multiple antennae results in synergistically larger zones of coagulation necrosis. *Ann Surg Oncol* 2003;**10**:275–83.
159. Kuang M, Lu MD, Xie XY, Xu HX, Mo LQ, Liu GJ. Liver cancer: increased microwave delivery to ablation zone with cooled-shaft antenna - experimental and clinical studies. *Radiology* 2007;**242**:914–24.
160. Tanaka K, Shimada H, Nagano Y, Endo I, Sekido H, Togo S. Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver. *Surgery* 2006;**139**:263–73.
161. Liang P, Dong B, Yu D, et al. Prognostic factor for percutaneous microwave coagulation therapy of hepatic metastases. *Am J Roentgenol* 2003;**181**:1319–25.
162. Shibata T, Murakami T, Ogata N. Percutaneous microwave coagulation therapy for patients with primary and

metastatic hepatic tumors during interruption of hepatic blood flow. *Cancer* 2000;**88**(2):302–11.
163. Matsukawa T, Yamashita Y, Arakawa A, et al. Percutaneous microwave coagulation therapy in liver tumors. A 3-year experience. *Acta Radiol* 1997;**38**(3):410–5.
164. Thomsen S. Pathologic analysis of photothermal and photomechanical effects of laser-tissue interactions. *Photochem Photobiol* 1991;**53**(6):825–35.
165. Hunter JG, Dixon JA. Lasers in cardiovascular surgery–current status. *West J Med* 1985;**142**(4):506–10.
166. Welch AJ, Motamedi M, Rastegar S, LeCarpentier GL, Jansen D. Laser thermal ablation. *Photochem Photobiol* 1991;**53**(6):815–23.
167. Ritz JP, Lehmann KS, Zurbechen U, et al. Improving laser-induced thermotherapy of liver metastases: effect of arterial microembolisation and complete blood flow occlusion. *Eur J Surg Oncol* 2007;**33**:608–15.
168. Pacella CM, Valle D, Bizzari G, et al. Percutaneous laser ablation in patients with isolated unresectable liver metastases form colorectal cancer. *Results of a Phase II study. Acta Oncol* 2006;**45**:77–83.
169. Christophi C, Nikfarjam M, Malcontenti-Wilson C, Muralidharan V. Long-term survival of patients with unresectable colorectal liver metastases treated by percutaneous interstitial liver thermotherapy. *W J Surg* 2004;**28**:987–94.
170. Vogl TJ, Straub R, Eichler K, Sollner O, Mack MG. Colorectal carcinoma metastases in liver: laser-induced interstitial thermotherapy: local tumour control rate and survival data. *Radiology* 2004;**230**:450–8.
171. Vogl TJ, Eichler KC, Straub R. Laser-induced thermotherapy of malignant liver tumours: general principles, equipments, procedures- side effects, complications and results. *Eur J Ultrasound* 2001;**13**:117–27.
172. Shankar A, Lees WR, Gillams AR, Ledermann J, Taylor I. Treatment of recurrent colorectal liver metastases by interstitial laser photocoagulation. *Br J Surg* 2000;**87**:298–300.
173. Gillams AR, Lees WR. Survival after percutaneous, image-guided, thermal ablation of hepatic metastases from colorectal cancer. *Dis Colon Rectum* 2000;**43**:656–61.
174. Caspani B, Cecconi P, Bottelli R, Della Vigna P, Ideo G, Gozzi G. The interstitial photocoagulation with laser light of liver tumors. *Radiol Med (Torino)* 1997;**94**(4):346–54.
175. Gillams AR, Brookes J, Hare C. Follow up of patients with metastatic liver lesions treated with interstitial laser therapy. *Br J Cancer* 1997;**196**:31.
176. Tranberg KG, Moller PH, Hannesson P, Stenram U. Interstitial laser treatment of malignant tumours: initial experience. *Eur J Surg Oncol* 1996;**22**(1):47–54.
177. Amin Z, Donald JJ, Masters A, et al. Hepatic metastases: interstitial laser photocoagulation with real-time US monitoring and dynamic CT evaluation of treatment. *Radiology* 1993;**187**(2):339–47.
178. Nolsoe CP, Torp-Pedersen S, Burcharth F, et al. Interstitial hyperthermia of colorectal liver metastases with a US-guided Nd-YAG laser with a diffuser tip: a pilot clinical study. *Radiology* 1993;**187**(2):333–7.
179. Amin Z, Bown SG, Lees WR. Local treatment of colorectal liver metastases: a comparison of interstitial laser photocoagulation (ILP) and percutaneous alcohol injection (PAI). *Clin Radiol* 1993;**48**(3):166–71.
180. Giorgio A, Tarantino L, de Stefano G, et al. Interstitial laser photocoagulation under ultrasound guidance of liver tumors: results in 104 treated patients. *Eur J Ultrasound* 2000;**11**(3):181–8.
181. Vogl TJ, Straub R, Eichler KC. Malignant liver tumours treated with MR imaging-guided laser-induced thermotherapy: experience with complications in 899 patients. *Radiology* 2002;**225**:367–77.
182. Cuschieri A, Crosthwaite G, Shimi S, et al. Hepatic cryotherapy for liver tumors. Development and clinical evaluation of a high-efficiency insulated multi-needle probe system for open and laparoscopic use. *Surg Endosc* 1995;**9**(5):483–9.
183. Silverman SG, Tuncali K, Adams DF, et al. MR imaging-guided percutaneous cryotherapy of liver tumors: initial experience. *Radiology* 2000;**217**(3):657–64.
184. Ruers T, Joosten J, Wiering B, et al. Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study. *Ann Surg Oncol* 2007;**14**:1161–9.
185. Brookes J, Wang F, Alfredson M, Yan TD, Morris DL. Synchronous liver resection for colorectal metastases: survival analysis. *Surgeon* 2005;**3**:265–8.
186. Seifert JK, Springer A, Baier P, Junginger T. Liver resection or cryotherapy for colorectal liver metastases: a prospective case control study. *Intl J Colorect Dis* 2005;**20**:507–20.
187. Seifert JK, Junginger T. Cryotherapy for liver tumours: current status, perspectives, clinical results and review of the literature. *Technol Cancer Res* 2004;**3**:151–63.
188. Mala T, Edwin B, Mathisen O, et al. Cryoablation of colorectal liver metastases: minimally invasive tumour control. *Scand J Gastroenterol* 2004;**39**:571–8.
189. Yan DB, Clingan P, Morris DL. Hepatic cryotherapy and regional chemotherapy with or without resection for liver metastases from colorectal carcinoma: how many are too many? *Cancer* 2003;**98**:320–30.
190. Rivoire M, De Cian F, Meeus P, Negrier S, Sebban H, Kammerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002;**95**:2283–92.
191. Seifert JK, France MP, Zhao J, et al. Large volume hepatic freezing: association with significant release of the cytokines interleukin-6 and tumor necrosis factor a in a rat model. *World J Surg* 2002;**26**(11):1333–41.
192. Sheen AJ, Poston GJ, Sherlock DJ. Cryotherapeutic ablation of liver tumours. *Br J Surg* 2002;**89**(11):1396–401.
193. Shimonov M, Shechter P, Victoria F, Ada R, Henri H, Czerniak A. Laparoscopic cryoablation of liver tumors. *Harefuah* 2002;**141**(5):414–7. p. 150.
194. Ruers TJM, Joosten J, Jager GJ, Wobbes T. Long-term results in treating colorectal metastases with cryosurgery. *Br J Surg* 2001;**88**:844–9.
195. Bilchik AJ, Wood TF, Allegra D. Al E. Cryosurgical ablation and radiofrequency ablation for unresectable hepatic malignant neoplasms. A proposed algorithm. *Arch Surg* 2000;**135**:657–64.
196. Chung MH, Ye W, Ramming KP, Bilchik AJ. Repeat hepatic cryotherapy for metastatic colorectal cancer. *J Gastrointest Surg* 2001;**5**(3):287–93.
197. Seifert JK, Achenbach T, Heintz A, Bottger TC, Junginger T. Cryotherapy for liver metastases. *Int J Colorectal Dis* 2000;**15**(3):161–6.
198. Junginger T, Seifert JK, Weigel TF, Heintz A, Kreitner KF, Gerharz CD. Cryotherapy of liver metastases. Initial results. *Med Klin* 1998;**93**(9):517–23.
199. Weaver ML, Ashton JG, Zemel R. Treatment of colorectal liver metastases by cryotherapy. *Semin Surg Oncol* 1998;**14**(2):163–70.
200. Hewitt PM, Dwerryhouse SJ, Zhao J, Morris DL. Multiple bilobar liver metastases: cryotherapy for residual lesions after liver resection. *J Surg Oncol* 1998;**67**(2):112–6.

201. Wallis CB, Coventry DM. Anaesthetic experience with laparoscopic cryotherapy. A new technique for treating liver metastases. *Surg Endosc* 1997;**11**(10):979–81.
202. Seifert JK, Morris DL. World survey on the complications of hepatic and prostate cryotherapy. *World J Surg* 1999;**23**(2):109–13. discussion 113-4.
203. Wemyss-Holden SA, Dennison AR, Finch GJ, Hall Pde Pde L, Maddern GJ. Electrolyte ablation as an adjunct to liver resection: experimental studies of predictability and safety. *Br J Surg* 2002;**89**:579–85.
204. Tsukioka T, Nishiyama N, Iwata T, Nagano K, Izumi N, Mizuguchi S, Morita R, Inoue K, Suehiro S. Pulmonary metastasis from colorectal carcinoma with hepatic metastasis. *Gen Thorac Cardiovasc Surg* 2007;**55**:455–60.
205. Abitabile P, Harti U, Lange J, Maurer CA. Radiofrequency ablation permits an effective treatment for colorectal liver metastases. *Eur J Surg Oncol* 2007;**33**:67–71.
206. Kosari K, Gomes M, Hunter D, Hess DJ, Greeno E, Sielaff TD. Local, intrahepatic, and systemic recurrence patterns after radiofrequency ablation of hepatic malignancies. *Gastrointest Surg* 2002;**6**:255–63.
207. Machi J, Uchida S, Sumida K, Limm WM, Hundahl SA, Oishi AJ, Furumoto NL, Oishi RH. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. *J Gastrointest Surg* 2001;**5**:477–89.
208. Jiao LR, Hansen PD, Havlik R, Mitry RR, Pignatelli M, Habib N. Clinical short-term results of radiofrequency ablation in primary and secondary liver tumors. *Am J Surg* 1999;**177**:303–6.
209. Beppu T, Ogawa M, Matsuda T, Ohara C, Hirota M, Shimada S, Yamaguchi Y, Yamanaka T. Efficacy of microwave coagulation therapy (MCT) in patients with liver tumors. *Gan To Kagaku Ryoho* 1998;**25**:1358–61.